

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ./.	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/02521	International filing date (day/month/year) 29/06/2000	Priority date (day/month/year) 08/07/1999
International Patent Classification (IPC) or national classification and IPC A61B5/00		
Applicant THE VICTORIA UNIVERSITY OF MANCHESTER et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 07/02/2001	Date of completion of this report 23.10.2001
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I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-11 as originally filed

Claims, No.:

1-14 with telefax of 28/09/2001

Drawings, sheets:

1/8-8/8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

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☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-14
	No: Claims
Inventive step (IS)	Yes: Claims 1-14
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-14
	No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. As amended claims 1-14 filed on 28.09.2001 do not contain subject-matter which extends beyond the content of the application as originally filed, they can be considered to meet the requirements of Article 34(2)(b)PCT.

2. Reference is made to the following document:

D1: US-A-5 571 893 (J. BAKER ET AL.) 5 November 1996 (1996-11-05)

3. As the particular combination of features of independent claim 1 is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel (Article 33(2) PCT).

4. Moreover, the subject-matter of the said claim 1 would appear to involve an inventive step in the sense of Article 33(3) PCT.

The closest state of the art document results from D1.

The said document discloses "CHF" ("cardiac hypertrophy factor" or "cardiotrophin-1(CT-1)") sequences isolated from murine embryoid bodies and its human equivalent (column 5, lines 53-67). The said murine and human CHF's having, among others, hypertrophic activity (column 16, lines 4-7). CHF can be used to increase physiological (beneficial) forms of hypertrophy and CHF antagonist to decrease pathological hypertrophy (column 7, lines 24-33).

D1 further teaches that the isolated CHF from mouse embryoid bodies (example I) is expected to improve cardiac hypertrophy when injected to rats (example II, column 64, lines 20-25) and that it is reasonable to expect that similar results may be obtained in humans (column 64, lines 32-41).

The subject-matter of claim 1 is distinguished therefrom in that cardiotrophin-1 is assayed in a sample of human bodily fluid.

The technical effect being the diagnosis or the detection of a predisposition to cardiac hypertrophy.

The technical problem to be solved by the invention was therefore to provide a

method for diagnosing or detecting a predisposition to cardiac hypertrophy.

The said problem has convincingly been solved by the applicant's discovery that the known CT-1 is suitable as **a marker** for diagnosing or detecting a predisposition to cardiac hypertrophy.

Other known molecule such as α -adrenergic transmitters, endothelin or atrial natriuretic factor (ANF) are known to be expressed in cardiac hypertrophy.

However, plasma level of these agents vary greatly in response to a whole range of factors over short period of time. Accordingly, these agents are not reliable markers for identifying the existence of, or a predisposition to, cardiac hypertrophy.

CT-1 presents the unexpected effect of being produced at the onset of, and during the complete cycle of disease progression and that the level of production does not fluctuate greatly. Moreover, the applicant has shown that the said molecule is present in human bodily fluids, thus facilitating its assay.

Thus, CT-1 cannot be considered as a mere selection among other known molecules expressed in cardiac hypertrophy.

The above mentioned document D1, which discloses the involvement of CT-1 in cardiac hypertrophy and its use or the use of CT-1 antagonists in various methods of treatment, does not disclose, nor suggest the use of the said CT-1 in a method for diagnosing or detecting a predisposition to cardiac hypertrophy.

D1 does not suggest any advantage of CT-1 over the other above mentioned known molecules. The skilled man, equipped with the teaching of D1, would not have any expectation of success in using CT-1 as a marker.

As D1 does not give any incentive to the skilled man to choice CT-1 as a marker for diagnosing or detecting a predisposition to cardiac hypertrophy, the subject-matter of claim 1 involves an inventive step in the sense of Article 33(3) PCT.

The same applies to dependent claims 2 to 12.

5. The subject-matter of independent claim 13 relates to the use of the above mentioned new and inventive method to determine human subjects who should be treated for hypertension. Cardiac hypertrophy being induced by hypertension, the assay of the marker CT-1 in the method of claim 13 is similarly new (Art. 33(2) PCT) and involves an inventive step (Art. 33(2) PCT).

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The subject-matter of independent claim 14, wherein the marker CT-1 is assayed for determining the efficacy of a treatment for hypertension is also new (Art. 33(2) PCT) and involves an inventive step (Art. 33(3) PCT).

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

Re Item VIII

Certain observations on the international application

1. The term "*in vitro* assay is arranged to detect..." used in claims 7 and 9 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

CLAIMS:

1. A method for diagnosing or detecting a predisposition to cardiac hypertrophy comprising assaying a sample of human bodily fluid *in vitro* for the level of cardiotrophin-1 (CT-1) contained in the sample and wherein elevated CT-1 levels are indicative of cardiac hypertrophy.
2. A method according to claim 1 in which diagnosis or detection of a predisposition to cardiac hypertrophy is determined by comparison of basal CT-1 levels from a human bodily fluid sample from a subject unaffected by cardiac hypertrophy and the level of CT-1 in a human bodily fluid sample of a subject under test.
3. A method according to claim 1 in which diagnosis or detection of a predisposition to cardiac hypertrophy is determined by comparison of basal CT-1 levels from a human bodily fluid sample previously taken from a subject under test and the level of CT-1 in a human bodily fluid sample of same subject under test.
4. A method according to claim 1 or 2 in which elevated CT-1 levels are indicative of the initiation or onset of cardiac hypertrophy.
5. A method according to claim 3 in which elevated CT-1 levels are indicative of developing cardiac hypertrophy.
6. A method according to any preceding claim in which the human bodily fluid sample comprises whole blood, plasma, serum, urine, tears, sputum, saliva or synovial fluid.

7. A method according to any preceding claim in which the *in vitro* assay is arranged to detect CT-1 protein or fragments thereof.
8. A method according to claim 7 in which the *in vitro* assay comprises radio immuno assay or enzyme-linked immunosorbant assay.
9. A method according to any one of claims 1 to 5 in which the *in vitro* assay is arranged to detect CT-1 nucleic acid or fragments thereof.
10. A method according to claim 9 in which the *in vitro* assay comprises hybridisation, sequencing or amplification techniques.
11. A method according to any preceding claim further comprising an *in vitro* assay for an additional marker.
12. A method according to claim 11 in which the additional marker is selected from ANF, oncostatin M, ciliary neurotrophic factor and leukaemia inhibiting factor.
13. Use of a method according to claim 1 to determine human subjects who should be treated for hypertension.
14. A method for determining the efficacy of treatment for hypertension comprising assaying a sample of human bodily fluid *in vitro* for the level of cardiotrophin-1 (CT-1) contained in the sample and wherein reduced CT-1 levels are indicative of an efficacious treatment.